IN THE CLAIMS

Claim 1(original): A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:
determining a level and/or an activity of

(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product

in a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

Claim 2(original): A method of monitoring the progression of a neurodegenerative disease in a subject, comprising:
determining a level and/or an activity of

(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

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(iii)   a fragment, or derivative, or variant of said
          transcription or translation product
          in a sample obtained from said subject and comparing
          said level and/or said activity to a reference value
          representing a known disease or health status,
          thereby monitoring the progression of said
          neurodegenerative disease in said subject.

Claim 3(original): A method of evaluating a treatment for a
neurodegenerative disease, comprising:
determining a level and/or an activity of
(i) a transcription product of a gene coding for a vault
     protein, the minor vault protein ADPRTL1, and/or
(ii) a translation product of a gene coding for a vault
     protein, the minor vault protein ADPRTL1, and/or
(iii)   a fragment, or derivative, or variant of said
         transcription or translation product,
in a sample obtained from a subject being treated for said
disease and comparing said level and/or said activity to a
reference value representing a known disease or health status,
thereby evaluating said treatment for said neurodegenerative
disease.

Claim 4(currently amended): The method according to claim 1 ~~any
of claims 1 to 3~~ wherein said neurodegenerative disease is
Alzheimer's disease.

Claim 5(currently amended): The method according to claim 1 ~~any
of claims 1 to 4~~ wherein said sample comprises a cell, or a
tissue, or a body fluid, in particular cerebrospinal fluid or
blood.

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Claim 6(currently amended): The method according to <u>claim 1</u> <s>any of claims 1 to 5</s> wherein said reference value is that of a level and/or an activity of

(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii)   a fragment, or derivative, or variant of said transcription or translation product,
in a sample obtained from a subject not suffering from said neurodegenerative disease.

Claim 7(currently amended): The method according to <u>claim 1</u> <s>any of claims 1 to 6</s> wherein an alteration in the level and/or activity of a transcription product of the gene coding for the minor vault protein ADPRTL1 and/or a translation product of a gene coding for the minor vault protein ADPRTL1, and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, obtained from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.

Claim 8(original): A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease by:
(i) detecting in a sample obtained from said subject a level,

or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, compared to a reference value representing a known health status; and said kit comprising:

a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and (ii) reagents that selectively detect a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1.

Claim 9(original): A method of treating or preventing a neurodegenerative disease, in particular AD, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of

(i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

Claim 10(original): A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) a gene coding for a vault protein, the minor vault protein

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ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault
     protein, the minor vault protein ADPRTL1, and/or
(iii)   a translation product of a gene coding for a vault
     protein, the minor vault protein ADPRTL1, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

Claim 11(original): A recombinant, non-human animal comprising
a non-native gene sequence coding for a vault protein, the
minor vault protein ADPRTL1, or a fragment, or a derivative, or
a variant thereof, said animal being obtainable by:

(i)   providing a gene targeting construct comprising said gene
      sequence and a selectable marker sequence, and

(ii) introducing said targeting construct into a stem cell of a
      non-human animal, and

(iii)   introducing said non-human animal stem cell into a
      non-human embryo, and

(iv) transplanting said embryo into a pseudopregnant non-human
      animal, and

(v)   allowing said embryo to develop to term, and

(vi) identifying a genetically altered non-human animal whose
      genome comprises a modification of said gene sequence in
      both alleles, and

(vii)   breeding the genetically altered non-human animal of
      step (vi) to obtain a genetically altered non-human animal

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whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

Claim 12(original): The animal according to claim 11 wherein said minor vault protein ADPRTL1 is the minor vault protein of SEQ ID NO. 2.

Claim 13(currently amended): Use of the recombinant, non-human animal according to claim 11 ~~or 12~~ for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

Claim 14(original): An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i)   a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii)   a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii), said method comprising:
(a)   contacting a cell with a test compound;
(b)   measuring the activity and/or level of one or more

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substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and

(d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

Claim 15(original): A method of screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i)   a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii)   a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii)   a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(v)   a fragment, or derivative, or variant of (i) to (iii), said method comprising:

(a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

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(b) measuring the activity and/or level of one or more
     substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more
     substances recited in (i) or (iv) in a matched
     control animal which is predisposed to developing or
     has already developed symptoms of a neurodegenerative
     disease or related diseases or disorders in respect
     to the substances recited in (i) to (iv) and to which
     animal no such test compound has been administered;

(d) comparing the activity and/or level of the substance
     in the animals of step (b) and (c), wherein an
     alteration in the activity and/or level of substances
     in the test animal indicates that the test compound
     is a modulator of said diseases or disorders.

Claim 16(original): The method according to claim 15 wherein
said test animal and/or said control animal is a recombinant
animal which expresses a vault protein, the minor vault protein
ADPRTL1 or a fragment, or a derivative, or a variant thereof,
under the control of a transcriptional control element which is
not the native vault protein gene transcriptional control
element.

Claim 17(original): An assay for testing a compound, preferably
for screening a plurality of compounds for inhibition of
binding between a ligand and a vault protein, the minor vault
protein ADPRTL1 or a fragment, or derivative, or a variant
thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said vault protein, or a
     fragment, or a derivative, or a variant thereof, to a
     plurality of containers;

(ii) adding a compound, preferably a plurality of compounds, to

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be screened for said inhibition of binding to said plurality of containers;

(iii)   adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;

(iv) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds, and said ligand;

(v) measuring amounts of detectable ligand or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and

(vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said vault protein, or said fragment, or derivative, or variant thereof.

Claim 18(original): An assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to a vault protein, the minor vault protein ADPRTL1, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i)   adding a liquid suspension of said vault protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;

(iii)   incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds;

(iv) measuring amounts of detectable compound or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and

(v) determining the degree of binding by one or more of said compounds to said vault protein, or said fragment, or derivative, or variant thereof.

Claim 19(original): Use of a protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

Claim 20(original): Use of a protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

Claim 21(original): Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample obtained from a subject, comprising

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immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell, and wherein said pathological state relates to a neurodegenerative disease, in particular Alzheimer's disease.